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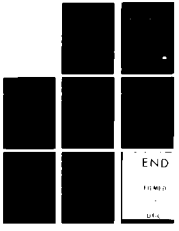

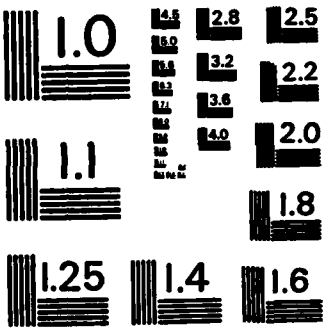

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Report SAM-TR-82-27

BIOCHEMICAL CHANGES IN BLOOD COMPONENTS AFTER LETHAL DOSES OF RADIATION

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October 1982

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Prepared for
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NOTICES

This final report was submitted by the New York State Department of Health, Albany, New York 12201, under contract F33615-78-D-0617, job order 7757-05-49, with the USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas. Captain Thomas E. Dayton was the Laboratory Project Scientist-in-Charge.

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The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act of 1970 and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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Nonpeptide, peptide, and protein blood components were measured postirradiation in Wistar rats to investigate biochemical changes that might be related to or form the basis of radiation-induced emesis. The rats were irradiated with lethal doses of radiation, and blood components were analyzed at various times postirradiation. The blood-component levels were compared to those of nonirradiated controls to determine if any significant changes occurred due to the radiation.

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20. ABSTRACT (Continued)

After irradiation, the following were noted: None of the peptides analyzed demonstrated significant changes; of the nonpeptide blood components, glucose and thromboxane B_2 showed significant changes ($p<.05$); and a number of the proteins changed significantly, including adrenocorticotropin, calcitonin, insulin, β-endorphin, and gastrin. Interrelationships between the various blood components are discussed.

In addition to its effects upon blood histamine, the effects of radiation upon rat mast cells and human basophils were investigated. High doses of radiation had very little observable effect upon the spontaneous release of histamine or IgE- and non-IgE-mediated histamine release from mast cells and basophils.

BIOCHEMICAL CHANGES IN BLOOD COMPONENTS AFTER LETHAL DOSES OF RADIATION

INTRODUCTION

Emetic responses to ionizing radiation have been observed clinically in humans and experimentally in monkeys, dogs, and cats (1-3). Exposure to radiation is also associated with an early transient incapacitation resulting in a performance decrement that has been experimentally demonstrated in pigs, rats, and monkeys (4-6). Humoral mediators that are formed or released after irradiation have been proposed as a cause of radiation-induced nausea, emesis, and early transient incapacitation. This hypothesis, in part, stems from observations of animals, protectively head-shielded, that underwent early transient incapacitation and emetic responses after irradiation (7-9). These observations, in conjunction with investigations showing that the chemoreceptor trigger zone in the lateral region of the area postrema is central in mediating radiation-induced emetic responses, lend support to the idea of humoral agents effecting emesis postirradiation (10). In short, ablation of the chemoreceptor trigger zone prevents vomiting due to irradiation,indicating that interactions within the area postrema are necessary for emesis even when the area postrema is not directly irradiated. Even in the event of a peripheral area postrema autonomic communication, peripheral signals afferent to the area postrema could emanate from concentration changes of humoral neurotropic agents.

Exposure to radiation at high enough levels to cause episodes of vomiting, nausea, fatigue, or early transient incapacitation would most likely result in a performance decrement that could affect the survivability of aircrews or their ability to maintain mission-completion performance (11). The purpose of this study is to investigate preliminary biochemical evidence of humoral mediation in radiation-induced emesis or performance decrement. The main approach is to measure the levels of various blood components and determine whether they change with irradiation. Particular attention is given to radiation-induced changes in the blood levels of neuroendocrine and neuropeptide components. Results of this study were input into Dr. Carpenter's concurrent experiments investigating emetic mechanisms in dogs (SAM-TR-82-28).

EXPERIMENTAL METHODOLOGY

Subjects

Male and female Wistar rats (200-300 g) were obtained from colonies maintained by Griffen Laboratories of the New York State Department of Health, Guilderland, N. Y. The rats were housed in plastic cages on wood shavings and given free access to Wayne Lab-Blox F6 Chow (Allied Mills, Chicago, Ill.) and tap water. Twelve-hour dark and light periods and 22° to 25°C room temperature were maintained. For all experiments rats were matched in sex, weight, and age.

Irradiation Procedure

The rats were whole-body irradiated in a plastic constraining cylinder that rotated inside the chamber of an Isomedix Inc. Model $M^{137}Cs$ Gammator. The dose rate profile in the rotating chamber was determined by eight Perspex samples (type 4034K) which showed a γ-ray dose rate of 484 rads/min. Most of the rats were irradiated for 2 min for a total dose of 968 rads. Sham controls were rotated in the animal holder for 2 min without being introduced into the irradiating chamber. In some instances, sham controls were compared with nonrotated controls. No differences were detected between sham-rotated and nonrotated controls.

Bleeding

Blood samples were taken from ether-anesthetized rats. Depending upon the experiment, rats were bled either by cardiac puncture, from the portal vein, or from the abdominal aorta.

Preparation of Sera

Blood samples taken for sera were allowed to coagulate for 30 min at room temperature and then iced. The samples were centrifuged for 15 min at 900 g. The clear serum layer was aspirated off the cell layer and frozen (-20°C) until assayed.

Preparation of Plasma

Blood samples taken for plasma were made 10% in 0.1 M ethylenediamine tetraacetate (EDTA, Sigma) which contained 0.54 mg/ml of 1.10 phenanthroline (Sigma), 0.22 mg/ml of captropril (Capoten, Squibb), and 1 mg/ml of aprotinin (Trasylol, FBA Pharmaceuticals). The plasma samples were centrifuged and stored similar to sera samples.

Pretreatment of Rats for Blood Histamine Determinations

Rats bled for plasma-histamine determinations were pretreated by intramuscular injection with the diamine oxidase inhibitor aminoguanidine (Sigma) (2.5 mg/kg), the H_2 blocker metiamide (Smith, Kline and French) (10 mg/kg), and the H_1 blocker pyrilamine (Sigma) (2.5 mg/kg). The reagents were injected in a saline isotonic carrier (0.5 ml) 30 min before bleeding.

Histamine Release from Mast Cells

Peritoneal mast cells were harvested from rats as previously described (12). After several centrifugal washes the mast cells were suspended in a TRIS-buffered (pH 7.0) solution containing 120 mM Na^+, 25 mM TRIS, 5 mM K^+, 0.1 mM mg^{2+}, and 0.03% gelatin. Duplicate tubes of both irradiated and nonirradiated reaction mixtures were incubated at 37°C in the presence and absence of homologous sera. The tubes were subsequently iced and centrifuged, and the supernatants were decanted and assayed for histamine.

Histamine Release from Human Basophils

Peripheral blood was obtained by venipuncture from allergic donors. The blood was made relatively free of red cells by sedimentation at 1 g for 45 min at room temperature in dextran and EDTA (13). The leukocyte-rich supernatant was removed, and platelets and plasma constituents were washed from the leukocytes by two centrifugal washes for 8 min at 275 g at 5°C in TRIS buffer pH=7.4). The leukocyte cell button was then resuspended in a TRIS buffer containing 0.03% gelatin, 25 mM TRIS (pH=7.4), 125 mM Na^+, 5 mM K^+, 1 mM Mg^{2+}, and 0.8 mM Ca^{2+}. Duplicate irradiated and nonirradiated samples were incubated at 37°C in the presence and absence of homologous sera. The tubes were subsequently iced and centrifuged, and the supernatants were decanted and assayed for histamine.

Histamine Assay

The histamine was assayed by an automated spectrofluorometric technique (14). The extraction and fluorometric procedures were based on methods previously reported (15). The percentage of histamine release was calculated in excess of the blank. Histamine assays performed on plasma had proteins precipitated by perchloric acid. In cellular release experiments, blank tubes (lacking inducing agent) released less than 5% of the total histamine content.

Glucose Analyses

Glucose in serum was analyzed by a colorimetric reaction with o-toluidine (16). The blue-green o-toluidine-glucose complex was formed at a low pH at 100°C. The intensity of the color was measured spectrophotometrically at 630 nm. The glucose concentrations were interpolated from a standard curve.

Radioimmunoassays

The basic principle of the radioimmunoassay procedures was the competition between radioactive and nonradioactive antigen for a fixed number of antibody-binding sites (17). The nonradioactive antigen in the samples and a fixed amount of radioactive tracer were allowed to react with a constant amount of limiting antibody. Bound antigen was separated from free antigen by either double antibody precipitation or charcoal adsorption. When the amount of bound antibody and/or free radioactive antigen was determined, the sample values could be interpolated from a standard curve. Depending upon the individual assay, the radioimmunoassays were performed on plasma or sera. In some instances an extraction procedure was performed before assay.

Analysis of Data

Experiments analyzing blood components postirradiation were performed using groups of 5 rats per data point. The data are reported as a mean value $\pm$ the standard deviation (SD). One-way analysis of variance test (18) was performed on each set of data to determine significant differences between treatment groups. Sets of data whose probabilities were less than 5% for the null

hypothesis were considered significant and examined further using Dunnet's multiple comparison procedures (18) to determine if the significant differences occurred between a sample mean and control mean.

Format of Tables

The data presented in Tables 1-3 show the effects of radiation on the levels of nonprotein (Table 1), peptide (Table 2), and protein (Table 3) blood components. The components assayed are listed with the concentration units of the table values. The table values are the mean values ($\pm$ SD) from 5 animals. The rats were bled for plasma or sera by the abdominal aorta, portal vein, or cardiac puncture. Both male and female Wistar rats were used.

Whether or not the rats were fasted is indicated by Y (yes) or N (no). The total whole-body doses of radiation in rats are listed; the dose rate was constant at 484 rads/min. Control groups were not irradiated. The times indicate initiation of bleeding after completion of irradiation. For most experiments the rats were irradiated for 2 min, but in some for as long as 10 min. Therefore, the duration of irradiation would have to be added to the initiation of bleeding time to obtain the length of time from which the animal was first exposed to radiation. Also, the duration of the bleeding procedures varied from 3-6 min, so no blood samples were actually obtained in less than 6-8 min from when the animals were first exposed to radiation. Times for which no sample was taken are indicated by ND (not done). The p values, as compared to the control values, are shown below the table values of the analyzed components.

RESULTS

Radiation Effects on Levels of Nonprotein Blood Components

The histamine shown in Table 1 was assayed spectrofluorometrically as indicated in Experimental Methodology. The values in ng/ml were obtained by comparison with histamine standards. The table data show that at the times of bleeding initiation (10-90 min postirradiation), histamine in blood samples of the irradiated rats was not significantly different from that of the nonirradiated controls. Both the male and female rats were pretreated with H_1 and H_2 antagonists along with a histaminase inhibitor. However, degradation of histamine by histamine n-methyltransferase was not prevented.

Serum glucose levels were assayed as described in Experimental Methodology. The nonirradiated control values averaged 140 mg of glucose per 100 ml of serum. At the 120-min bleeding initiation time of the experiment with male rats, the sera glucose values dropped to 115 mg/100 ml--significantly less than the control value ($p < .05$).

The values reported in the two glucose experiments with female rats show how a bolus of glucose is metabolized postirradiation. Except for the controls, both groups were given a bolus of glucose (5 g/kg). The irradiated animals (2000 rads) were given the glucose bolus just prior to irradiation; the lower p values of this experiment show the significance level of its postirradiation

TABLE 1. CHANGES IN NONPROTEIN BLOOD COMPONENTS AFTER IRRADIATION

Assay	Bleeding[a]	Sex	Fasting	Rads 484/min	Control	Bleeding initiated postirradiation								
						0'	10'	15'	20'	30'	60'	90'	120'	240'
Histamine ng/ml	A/P	M	N	968	74±14	ND	68±14 p>.05	ND	95±15 p>.05	ND	ND	71±16 p>.05	ND	ND
Histamine ng/ml	A/P	F	N	968	85±31	ND	63±5 p>.05	ND	79±20 p>.05	ND	ND	76±31 p>.05	ND	ND
Glucose mg/100 ml	C/S	M	N	968	140±21	ND	ND	134±11 p>.05	ND	141±11 p>.05	122±10 p>.05	ND	115±7 p<.05*	ND
Glucose[b] mg/100 ml	C/S	F	N	2000	142±13	ND	ND	240±23 p<.5 p<.05*	ND	211±59 p>.5 p<.05*	155±21 p>.5 p>.05	ND	128±9 p<.01* p>.05	ND
Glucose[c] mg/100 ml	C/S	F	N	0	142±13	ND	ND	270±42 p<.05*	ND	188±46 p>.05	155±13 p>.05	ND	166±17 p>.05	ND
TXB_2 pg/ml	A/P	F	N	1000	186±257	ND	422±191 p>.05	ND	156±144 p>.05	660±329 p<.05*	276±342 p>.05	181±137 p>.05	ND	ND
6 Keto $PGF_{1\alpha}$ pg/ml	A/P	F	N	1000	92±83	ND	156±49 p>.05	ND	64±19 p>.05	171±154 p>.05	97±49 p>.05	50±13 p>.05	ND	ND
Cortisol ng/ml	C/S	M	N	968	19±12	12±3.4 p>.05	ND	ND	ND	19±8 p>.05	34±16 p>.05	19±10 p>.05	16±9 p>.05	15±6 p>.05
Cortisol ng/ml	C/S	F	N	968	12±9	18±10 p>.05	ND	ND	ND	12±7 p>.05	11±8 p>.05	12±6 p>.05	11±3 p>.05	12±7 p>.05

[a]Abdominal aorta (A); portal vein (V); cardiac (C); plasma (P); serum (S) - Times indicate minutes after irradiation or glucose bolus.

[b]Animals were force-fed a bolus of glucose (5 g/kg) just prior to irradiation; controls were not given a bolus and were not irradiated. Upper p values are obtained by comparing with nonirradiated animals given a bolus (c); lower p values are obtained by comparing with controls.

[c]Nonirradiated animals were given a bolus of glucose (5 g/kg); controls were not given a bolus.

*Significant difference from controls.

values (irradiation + glucose bolus) compared with its control value (no irradiation or bolus). As expected, in irradiated rats given a bolus, the 15-min bleeding initiation time yielded a serum glucose value (240 mg/100 ml) significantly higher ($p < .05$) than the control value. The upper p values of this experiment show the significance levels when comparing the effect in time on irradiated and nonirradiated animals when both groups were given a bolus of glucose. At 120 min postirradiation, the irradiated group had significantly lower serum glucose levels than the nonirradiated group (129 vs 166 mg/100 ml, $p < .01$). These data indicate that irradiation either lowers glucose secretion or increases the rate of glucose metabolism.

A major metabolite of the cyclooxygenase pathway of prostaglandin synthesis is thromboxane B_2 (TXB_2). The plasma TXB_2 values of Table 1 were obtained by radioimmunoassay using a tritiated TXB_2 as tracer. The values in pg/ml were obtained by interpolation from a standard curve. Another product that could result from cyclooxygenase activity is the prostaglandin metabolite 6-keto prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$). The plasma values in pg/ml of the 6-keto $PGF_{1\alpha}$ also were obtained by a radioimmunoassay using tritiated 6-keto $PGF_{1\alpha}$ as a tracer. Although both TXB_2 and 6-keto $PGF_{1\alpha}$ increase at the 30-min bleeding time, only the TXB_2 shows postirradiation values significantly different from the control values ($p < .05$).

Cortisol was assayed by an ^{125}I radioimmunoassay procedure. The serum cortisol values for both male and female irradiated rats did not significantly differ from their control (nonirradiated) values (Table 1). However, in the irradiated males a significant difference ($p < .05$) occurred between the zero time and 60-min cortisol levels. Also, the difference between cortisol levels of irradiated male and female rats appeared to be significant ($p < .05$) at 60 min.

Radiation Effects on Levels of Peptide Blood Components

The peptides listed in Table 2 were analyzed by radioimmunoassay using ^{125}I tracer for each component. Values were obtained by interpolations from standard curves.

Although most of the postirradiation peptide changes are not reported as significant, the magnitude of the differences from controls suggests that further investigation is needed.

Neurotensin levels appeared to differ significantly between some irradiated groups, but no irradiated group showed a significant difference ($p < .05$) from the control group.

Substance P mean levels tended to decline at about 90 min, but because standard deviations were very large, no significant difference was detected.

Mean somatostatin levels in male rats also declined at around 60 min; however, the standard deviation is large, rendering the change insignificant.

Angiotensin I levels at 30 min postirradiation increased in both males and females, relative to controls, but the difference was significant ($p < .05$) only in females receiving 968 rads. The mean control angiotensin I in male rats

TABLE 2. CHANGES IN PEPTIDE BLOOD COMPONENTS AFTER IRRADIATION

Assay	Bleeding[a]	Sex	Fasting	Rads 484/min	Control	Bleeding initiated postirradiation 0'	10'	15'	20'	30'	60'	90'	120'	240'
Neurotensin pg/ml	V/P	M	Y	968	41±4	ND	ND			40±5 p>.05	36±2 p>.05	44±4 p>.05	44±5 p>.05	ND
Neurotensin pg/ml	C/P	F	Y	968	21±10	ND		ND		20±6 p>.05	25±5 p>.05	25±10 p>.05	26±8 p>.05	ND
Neurotensin pg/ml	C/P	M	Y	968	21±10	ND		ND		19±6 p>.05	25±5 p>.05	25±10 p>.05	26±8 p>.05	ND
Substance P pg/ml	C/P	F	Y	968	272±222	ND		ND		383±253 p>.05	221±60 p>.05	ND	ND	ND
Substance P pg/ml	C/P	F	Y	968	493±351	ND		ND		ND	ND	260±114 p>.05	410±328 p>.05	ND
Substance P pg/ml	C/P	M	Y	968	609±498	ND		ND		646±562 p>.05	333±147 p>.05	245±167 p>.05	179±61 p>.05	ND
Somatostatin pg/ml	C/P	F	N	968	33±12	ND		ND		28±9 p>.05	30±8 p>.05	32±12 p>.05	27±13 p>.05	ND
Somatostatin pg/ml	C/P	M	N	968	30±14	ND		ND		26±9 p>.05	15±16 p>.05	18±13 p>.05	22±15 p>.05	ND
Angiotensin I ng/ml	C/P	F	N	4840	1.6±.8	0.85±0.6 p>.05		1.1±0.2 p>.05		ND	ND	ND	ND	ND
Angiotensin I ng/ml	C/P	F	N	4840	1.3±04	ND		ND		ND	1.2±0.6 p>.05	ND	0.8±0.2 p>.05	ND
Angiotensin I ng/ml	C/P	M	N	968	2.0±0.8	1.0±0.5 p>.05		ND		2.8±1.4 p>.05	2.4±0.9 p>.05	2.7±0.9 p>.05	1.8±0.6 p>.05	1.0±0.5 p>.05
Angiotensin I ng/ml	C/P	F	N	968	1.0±.5	1.0±0.7 p>.05		ND		2.0±0.9 p<.05*	1.1±0.6 p>.05	0.8±0.3 p>.05	1.1±0.4 p>.05	0.8±0.6 p>.05

[a]Portal vein (V); cardiac (C); plasma (P).

*Significant difference from controls.

decreased at zero time relative to the level of nonirradiated controls; treatment groups (30, 60, and 90 min) tended to remain elevated (but not significantly) longer above their control value than did female treatment groups above their control.

Radiation Effects on Levels of Protein Blood Components

Table 3 shows how some proteins found in blood vary postirradiation. All of the proteins were analyzed by radioimmunoassay, and the values were interpolated from standard curves.

At postirradiation times tested, the blood levels of the thyroid-stimulating hormone (TSH) showed no tendency to vary from the nonirradiated controls.

Mean values of adrenocorticotropin (ACTH) in males and females at 30 min postirradiation were double those of nonirradiated controls; but because of large standard deviations, the increases were not significant. A large discrepancy is seen between the male and female control values, and whether the plasma ACTH values from male rats drop at 60 min and then rise again at 120 min should be investigated further.

Although the calcitonin data show some significant postirradiation differences, the data as a whole are equivocal. The control values of the female-rat serum samples are considerably higher than the controls of the males. Also, at the 120-min postirradiation time, the mean value for the females (386 ± 93) is significantly lower ($p < .05$) than their control value (732 ± 181). Conversely, one experiment performed on male rats shows that at zero time and 120 min postirradiation, the calcitonin value was significantly higher ($p < .05$) than for the controls.

Serum insulin tended to decrease postirradiation; however, statistical analysis showed significant difference only in female-rat levels at 0, 30, 60, 90, and 120 min postirradiation. Large SDs in the male groups precluded finding any significant differences between controls and postirradiation groups. Whether the male rats were nonfasted or fasted did not seem to affect the postirradiation insulin levels.

Overall, the β-endorphin and lipoprotein data showed a tendency to be elevated between 10 and 30 min postirradiation, but statistical analysis of the data negated the significance of these increases. In these experiments, data reported as greater than 160 mol/liter were excluded from the statistical analysis because of no SDs; the SDs could not be determined since 160 mol/liter was the greatest concentration that could be determined using the prepared standards. Instead, a rank-sum test was performed on control- and treatment-group values (all of which were 160 mol/liter); results indicate that a significant difference may exist between 10 and 30 min and should be investigated further.

The gastrin values for male rats indicate a rise at about 90 min postirradiation that is significantly higher than the control value. The female-rat values show a rise in gastrin at 60 and 90 min postirradiation, but not of significance.

TABLE 3. CHANGES IN PROTEIN BLOOD COMPONENTS AFTER IRRADIATION

Assay	Bleeding[a]	Sex	Fasting	Rads 484/min	Control	Bleeding initiated postirradiation 0'	10'	15'	20'	30'	60'	90'	120'	240'
TSH pm/ml	C/P	M	N	968	6.8±1.0	ND	ND	7.4+0.9 p>.05	ND	7.5±1.0 p>.05	7.0+0.6 p>.05	ND	7.8+0.4 p>.05	ND
ACTH pg/ml	C/P	F	Y	968	530±214	ND	ND	ND	ND	914+490 p>.05	430+109 p>.05	580+131 p>.05	568+131 p>.05	ND
ACTH pg/ml	C/P	M	Y	968	123±79	ND	ND	ND	ND	245+238 p>.05	56±11.5 p>.05	132+76 p>.05	291+135 p>.05	ND
Calcitonin pg/ml	C/S	F	N	968	732±181	592+125 p>.5	ND	ND	ND	698+224 p>.05	630+186 p>.05	672+132 p>.05	386+93 p<.05*	512+160 p>.05
Calcitonin pg/ml	C/S	M	Y	968	206±57	ND	ND	ND	ND	ND	256+94 p>.05	197+41 p>.05	ND	ND
Calcitonin pg/ml	C/P	M	Y	968	234±78	ND	ND	ND	ND	157+13 p>.05	220+84 p>.05	ND	ND	ND
Calcitonin pg/ml	C/S	M	N	968	267±66	444+104 p<.05*	ND	ND	ND	370+55 p>.05	406+158 p>.05	413+68 p>.05	418+82 p<.05*	297+66 p>.05
Insulin pm/ml	C/S	M	N	968	15±5	13+4 p>.05	ND	ND	ND	10±12 p>.05	8±3 p>.05	9±2 p>.05	9±1 p>.05	10±12 p>.05
Insulin pm/ml	C/S	F	N	968	18±3	13±2 p<.05*	ND	ND	ND	13±3 p<.05*	13±2 p<.05*	13±4 p<.05*	12±1 p<.05*	16±2 p>.05
Insulin pm/ml	C/S	M	Y	968	16±12	ND	ND	ND	ND	ND	9±4 p>.05	9±1 p>.05	ND	ND

[a]Abdominal aorta (A); portal vein (V); cardiac (C); plasma (P); serum (S).

*Significant difference from controls.

(Table continued next page)

TABLE 3 (Continued).

Assay	Bleeding[a]	Sex	Fasting	Rads 484/min	Control	0'	10'	15'	20'	30'	60'	90'	120'	240'
β-endorphin lipoprotein mol/l	V/P	M	Y	968	86±49	ND	160[b] p<.05*	ND	104±49 p>.05	ND	86±47 p>.05	ND	ND	ND
β-endorphin lipoprotein mol/l	A/P	M	Y	968	93±50	ND	ND	ND	ND	160[b] p<.05*	133±46 p>.05	93±65 p>.05	90±43 p>.05	ND
β-endorphin lipoprotein mol/l	A/P	M	N	1000	145±37	ND	181±59 p>.05	ND	104±12 p>.05	124±34 p>.05	103±12 p>.05	125±39 p>.05	ND	ND
β-endorphin lipoprotein mol/l	V/P	M	N	1000	108±18	ND	121±29 p>.05	ND	135±28 p>.05	148±20 p>.05	124±27 p>.05	111±19 p>.05	ND	ND
Gastrin pg/ml	C/S	M	N	968	412±190	390±157 p>.05	ND	ND	ND	708±142 p>.05	368±196 p>.05	796±217 p<.05*	414±265 p>.05	708±289 p>.05
Gastrin pg/ml	C/S	F	N	968	337±211	332±107 p>.05	ND	ND	ND	260±153 p>.05	428±183 p>.05	385±317 p>.05	281±192 p>.05	214±134 p>.05
Prolactin ng/ml	C/S	F	Y	968	6.2±.5	ND	ND	ND	ND	6.4±.6 p>.05	6.1±.7 p>.05	6.3±.4 p>.05	6.1±1. p>.05	ND
Prolactin ng/ml	C/S	M	Y	968	6.6±.8	ND	ND	ND	ND	6.1±1.1 p>.05	6.5±.6 p>.05	6.4±.2 p>.05	5.9±.4 p>.05	ND

[a]Abdominal aorta (A); portal vein (V); cardiac (C); plasma (P); serum (S).

[b]Not used in one-way analysis of variance; however, control and treatment grouns compared using rank-sum test.

*Significant difference from controls.

In the serum prolactin measurements, the postirradiation values showed no significant difference from the control values.

Radiation Effect on Histamine Release from Rat Mast Cells

Figure 1 illustrates the effect of radiation upon in vitro release of histamine from peritoneal rat mast cells. The irradiated cells were exposed to radiation for 8 min at 37°C for a total of 3,872 rads. Both irradiated and nonirradiated cells were allowed to incubate at 37°C.

Compound 48/80 was added to irradiated and nonirradiated cells at the times indicated by the abscissa. After the inducing agent was added, the cells were incubated an additional 5 min, then removed, iced, and centrifuged; the supernatants were assayed for histamine. The data indicate that irradiated and nonirradiated rat mast cells respond similarly to 48/80-induced histamine release. The irradiated and nonirradiated blank tubes were removed from the 37°C incubation at the time indicated by the abscissa. They were subsequently centrifuged and the supernatants analyzed for released histamine. The irradiated and nonirradiated cells without inducing agent each released less than 1% of the total histamine content (1 μg/ml). The data indicate that peritoneal rat mast cells do not release significant amounts of histamine when directly irradiated in vitro even when incubated for 180 min postirradiation.

Radiation Effect on Anti-IgE-Induced Histamine Release from Human Basophils

Figure 2 shows the effect of radiation on anti-IgE-induced histamine release from human basophils in vitro. Increasing concentrations of anti-IgE (10^{-11}M to 10^{-7}M) were added to cells irradiated for 10 min (4,840 rads) and to nonirradiated cells. The Figure 2 data are plotted as percentage of histamine release versus the anti-IgE concentrations in the reaction mixtures. The percentage of histamine release was calculated in excess of the blank. Blank tubes, without anti-IgE, released less than 5% of the total histamine content from both irradiated and nonirradiated cells. The total histamine content for tubes in which all cells were lysed was approximately 150 ng of histamine per ml.

Irradiated and nonirradiated basophils showed very little difference in their response to low doses of anti-IgE (10^{-11}M). At higher doses, however, the irradiated cells released higher percentages of histamine than did the nonirradiated cells. Histamine-releasing cells can be rendered unresponsive by excess inducing agent (see Fig. 2, descending portion of dose-response curve), although irradiated cells are not as susceptible as the nonirradiated.

Histamine Content Released from Irradiated and Nonirradiated Rat Mast Cells

Peritoneal rat mast cells were irradiated in vitro for 5 min (2,420 rads) and then incubated up to 120 min at 37°C. Histamine was assayed at the nanogram level, and the amounts of histamine liberated by the irradiated and nonirradiated cells were compared (Fig. 3). Irradiated and nonirradiated cells each released less than 3% of the total histamine content over a 120-min incubation period. The total histamine content, for the completely lysed cells, was 4.7 μg/ml. The quantity of histamine in the supernatant for the

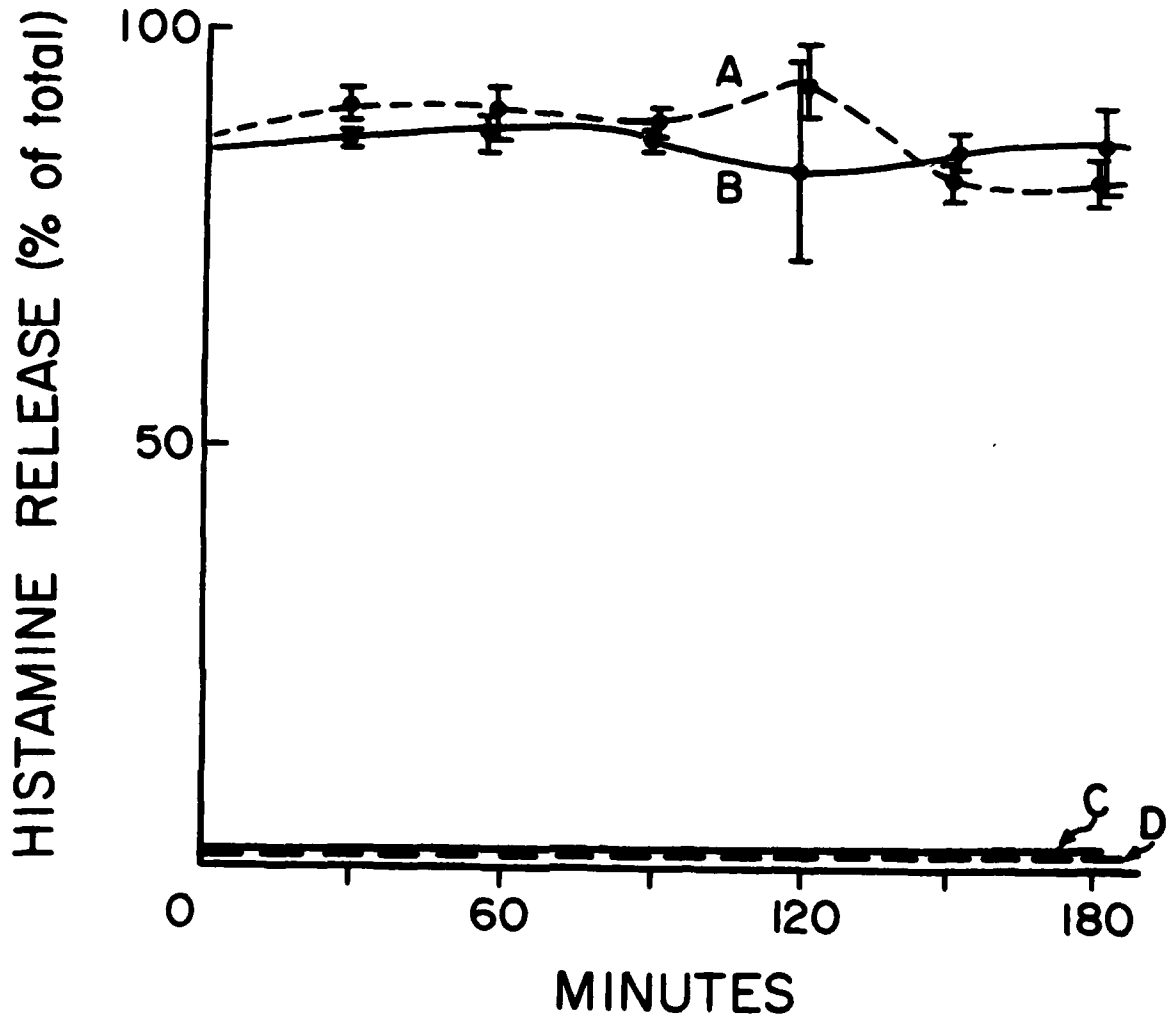

Figure 1. Radiation effect on compound-48/80-induced histamine release from Wistar rat peritoneal mast cells in vitro. Mast cells irradiated at 37°C in vitro (3,872 rads) are compared to non-irradiated cells. (A - irradiated cells; B - nonirradiated cells; C - nonirradiated blank; D - irradiated blank.) Cells (A & B) were challenged with compound 48/80 (1 μg/ml) at times indicated by the abscissa and incubated 5 min after the addition; the supernatants were analyzed for histamine. Blank tubes (C & D), with no compound 48/80 added, were removed from 37°C at the times indicated by the abscissa. The total histamine content was 1 μg/ml. Values are plotted with ranges.

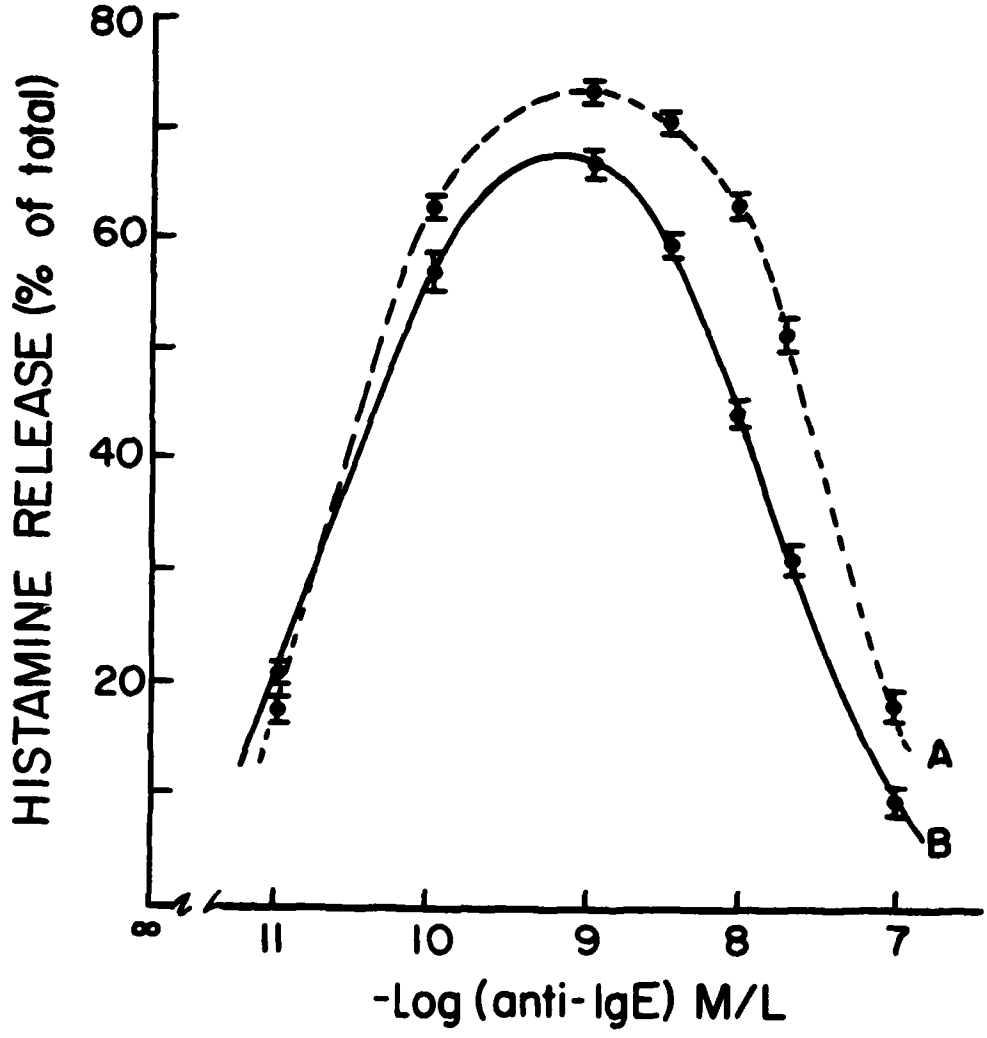

Figure 2. Radiation effect on anti-IgE-induced histamine release from human basophils in vitro. Human peripheral blood basophils were obtained by venipuncture. Irradiated cells (A--4,840 rads at 37°C) were compared to nonirradiated cells (B). After cells (A & B) were challenged in vitro with anti-IgE concentrations indicated by the abscissa, they were incubated for 40 min at 37°C; the supernatants were analyzed for histamine. Blank tubes released less than 5% of the 150 ng/ml total histamine content for all irradiated and nonirradiated cells. Values are plotted with ranges.

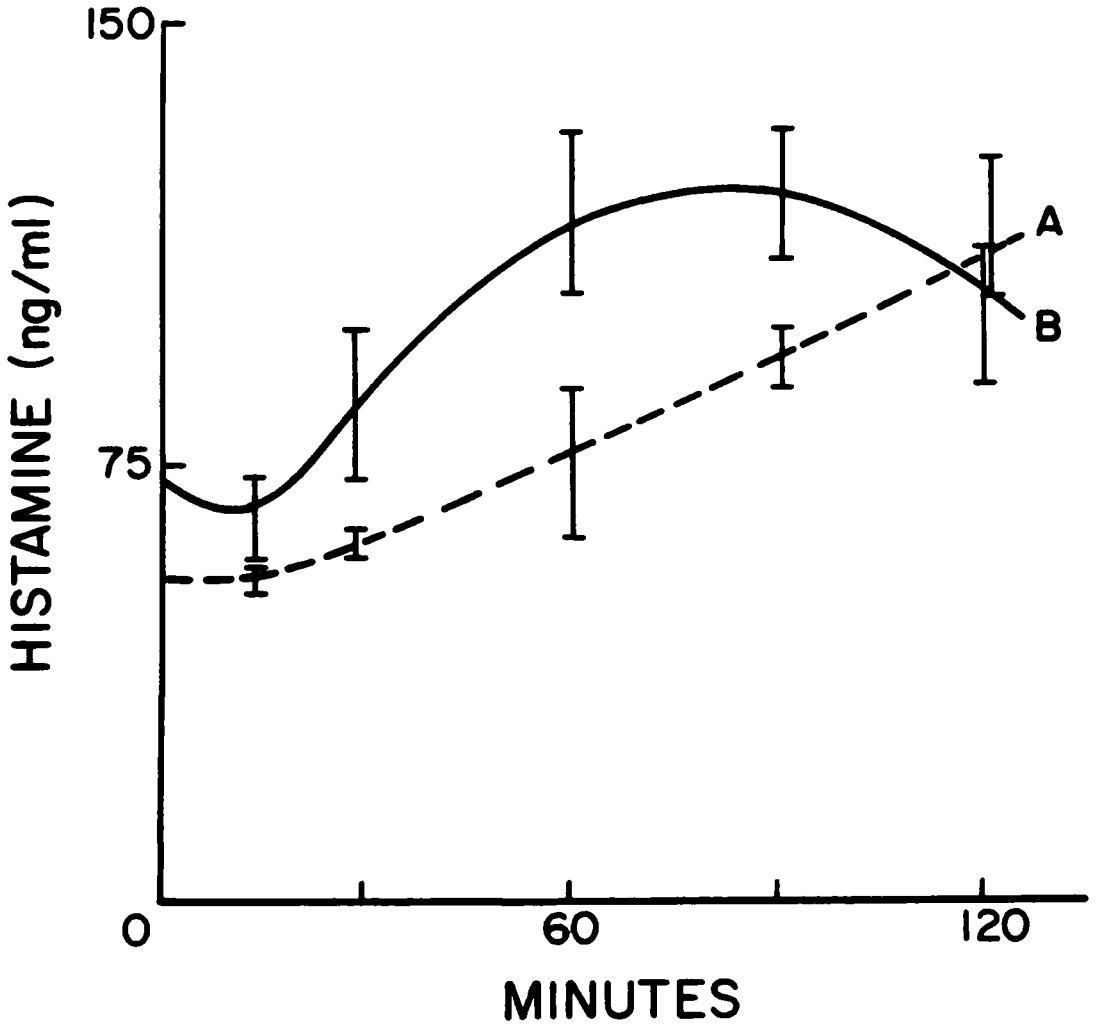

Figure 3. Radiation effect on spontaneous release of histamine from Wistar rat peritoneal mast cells in vitro. Mast cells irradiated at 37°C in vitro (2,420 rads) were compared to nonirradiated cells for spontaneously released histamine. (A - irradiated cells; B - nonirradiated cells.) All cells were incubated at 37°C for up to 120 min. The supernatants were analyzed at a high enough sensitivity (at the times indicated by the abscissa) to detect small differences in the histamine spontaneously released. Complete tubes, in which all the cells were lysed, contained a total histamine content of 4.7 μg/ml. Values are plotted with ranges.

irradiated and nonirradiated cells did not exceed 100 ng/ml. The spontaneous release of histamine from irradiated cells was not higher than that from nonirradiated cells.

Radiation Effect on Ionophore-Induced Histamine Release from Human Basophils

Figure 4 compares the ability of irradiated and nonirradiated cells to spontaneously release histamine, also to respond to a fixed dose of antigen-E (AgE) or ionophore A23187. Some cells were irradiated for 10 min (4,840 rads) in vitro at 37°C; the nonirradiated cells were parallel-incubated for 10 min at 37°C. Both groups were subsequently challenged with AgE (10^{-10}M) or ionophore A23187 (0.1 µg/ml) and incubated at 37°C for 40 min. Irradiated and nonirradiated blank tubes, without inducing agents, also were incubated at 37°C for 40 min. The blank tubes released less than 5% of the total histamine content. For the submaximum dose of AgE and of ionophore, the irradiated cells had a lower percentage release than the nonirradiated cells. At submaximum doses in other experiments, however, no consistent differences were seen between irradiated and nonirradiated cells in their response to inducing agent. Figure 4 shows that irradiated basophils do not spontaneously release significant quantities of histamine and are not rendered overly responsive or unresponsive to ionophore-A23187-induced histamine release as compared to nonirradiated basophils.

Irradiation of Human Basophils in the Presence of Serum and Plasma

Figure 5 compares the spontaneous release of histamine from irradiated and nonirradiated basophils in the presence of homologous plasma or serum. Cells were suspended in vitro in a TRIS saline-buffered solution that was 10% in plasma or serum. Cells were irradiated 2 min (968 rads) at 37°C. All cells were subsequently incubated for 60 min at 37°C. When compared, the quantity of histamine released spontaneously after irradiation in the presence of plasma or serum was similar to that released by the nonirradiated controls. The total histamine in the tube when all cells were lysed was 160 ng/ml. The histamine released spontaneously was less than 6% of the total histamine content. These data show that no factor in plasma or serum induces histamine release from human basophils irradiated in vitro.

Plasma Histamine Content Immediately Postirradiation

Histamine levels in plasma were measured spectrofluorometrically in irradiated and nonirradiated rats. Both groups were pretreated with aminoguanidine (10 mg/kg) and pyrilamine (20 mg/kg) 30 min before irradiation and bleeding. The irradiated rats received a fixed dose of 1,936 rads (4 min at 484 rads/min) and were bled by cardiac puncture immediately after irradiation, as described in Experimental Methodology. The plasma was made 2×10^{-4}M in aminoguanidine. The blood plasma histamine of the five irradiated rats showed no significant increase when compared to the five controls (Fig. 6). Two histamine determinations were made per rat.

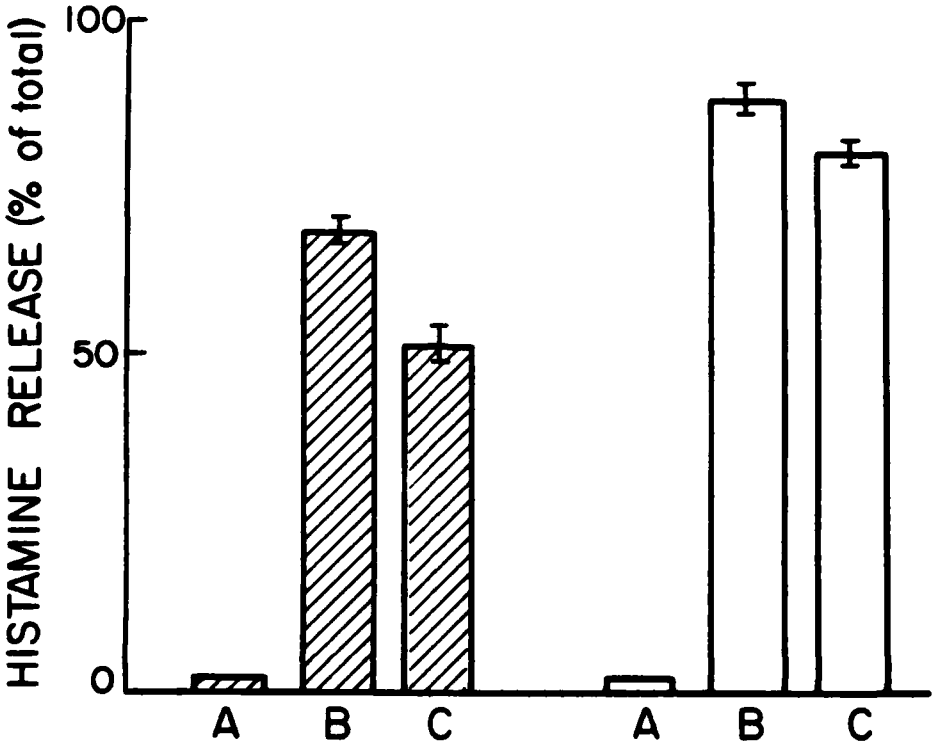

Figure 4. Radiation effect on antigen-E- or ionophore-A23187-induced histamine release from human basophils in vitro. Human basophils were obtained from peripheral blood by venipuncture. Cells were irradiated (4,840 rads) at 37°C in vitro. Irradiated (hatched bars) and nonirradiated (nonhatched bars) cells were compared in their ability to spontaneously release histamine (bars A) or to respond to antigen E (bars B) or ionophore A23187 (bars C). Cells challenged with a fixed dose of antigen E (10^{-10} M) or ionophore A23187 (0.1 μg/ml) were then incubated for 40 min at 37°C. Irradiated and nonirradiated blank tubes (bars A) were also incubated for 40 min but without any inducing agent. Complete tubes, in which all cells were lysed, contained a total histamine content of 180 ng/ml. Values are shown with ranges.

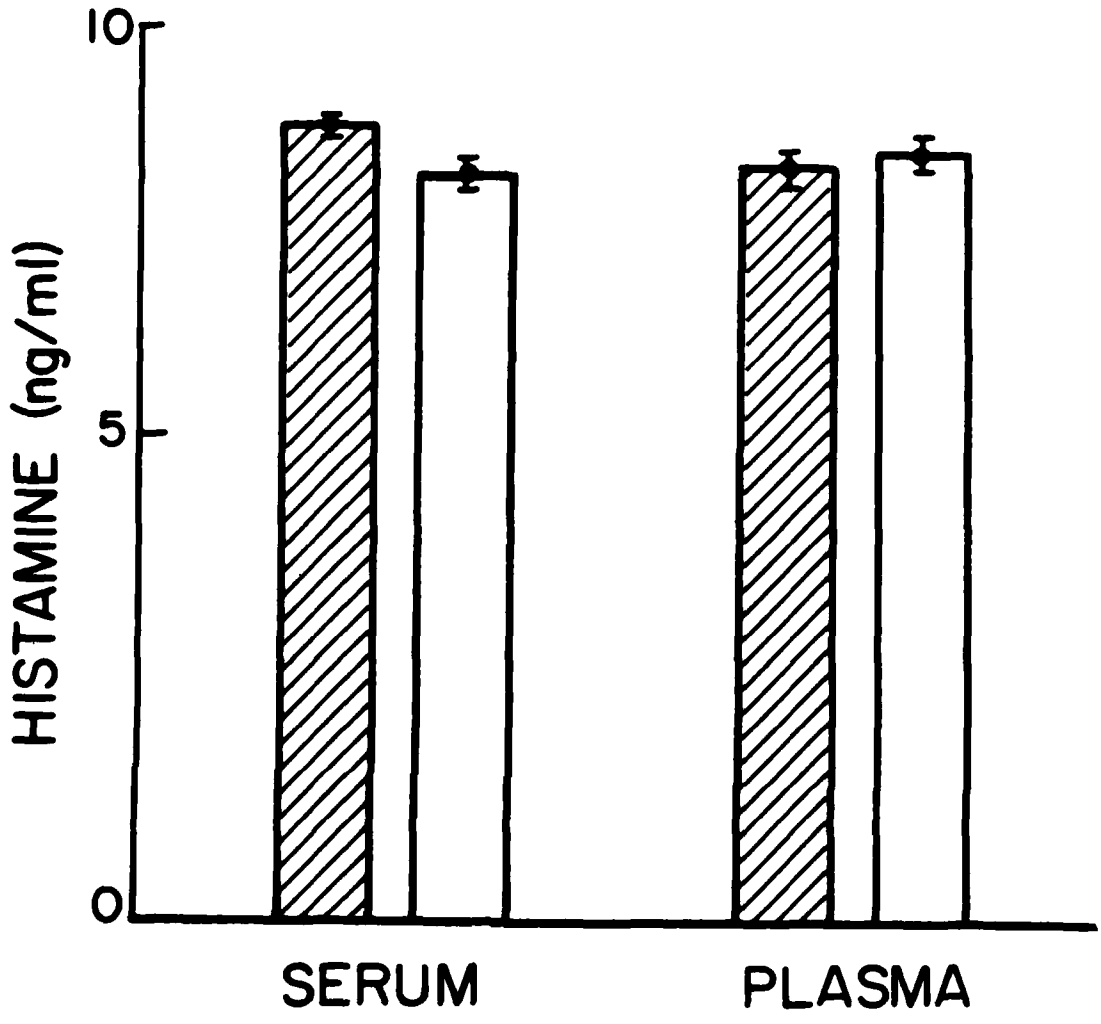

Figure 5. Radiation effect on spontaneous release of histamine from human basophils in vitro in the presence of plasma or serum. Human basophils were obtained from peripheral blood by venipuncture. Cells were irradiated 2 min (968 rads) at 37°C in vitro in the presence of 10% serum or plasma. Irradiated (hatched bars) and nonirradiated (nonhatched bars) cells were incubated with the serum or plasma for 60 min at 37°C. The supernatants were analyzed, at a high sensitivity, for spontaneously released histamine. Complete tubes, in which all cells were lysed, contained a total histamine content of 160 ng/ml. Values are shown with ranges.

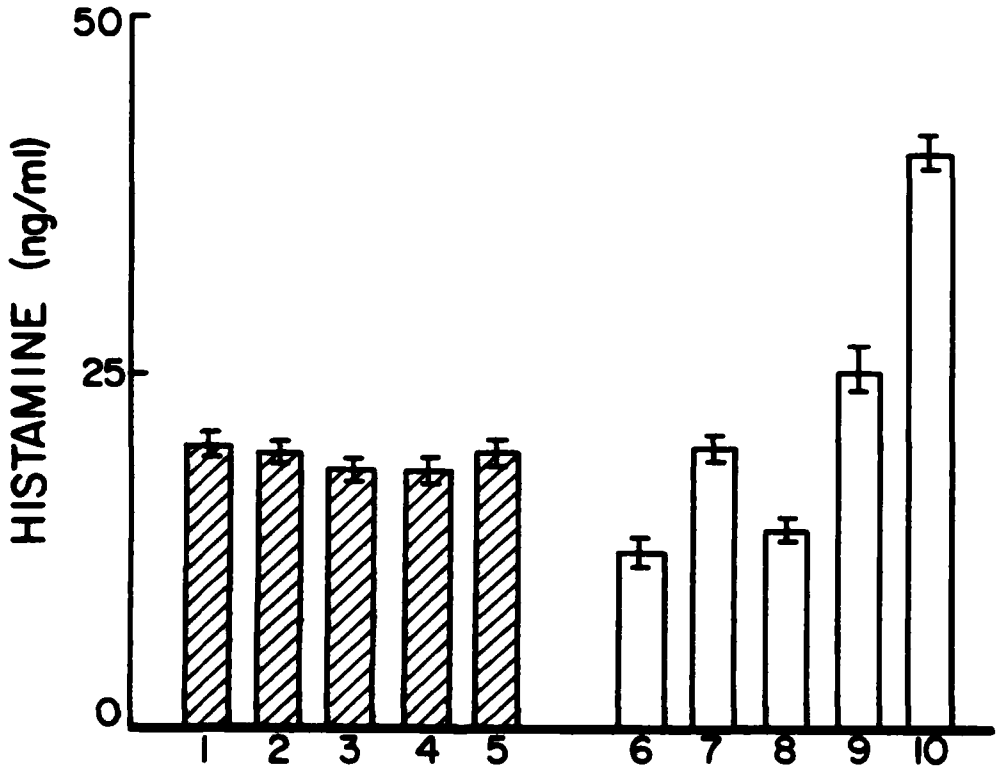

Figure 6. Histamine content in rat plasma immediately postirradiation. Five Wistar rats were irradiated (1,936 rads, 4 min at 484 rads/min) and immediately bled by cardiac puncture for plasma. The five irradiated samples (hatched bars) were compared with five nonirradiated controls (nonhatched bars). Proteins of the plasma samples were removed by perchloric acid precipitation. The deproteinated plasma samples were spectrofluorometrically analyzed for histamine. Values are shown with ranges.

DISCUSSION

Of the nonpeptide blood components analyzed in this report, histamine had previously received most attention. Some reports had suggested increases in blood histamine postirradiation (19-21) and radiation-induced mast cell degranulation (22). We were not able, however, to detect any radiation-induced mast cell or basophil degranulation or any significant changes in blood histamine postirradiation. Although histaminase inhibitors and H_1 and H_2 antagonists were used to prevent histamine uptake and degradation, the blood histamine experiments of this report should probably be repeated in the presence of histamine n-methyltransferase activity which is a primary pathway of histamine degradation (23).

One interesting aspect of our nonpeptide-blood-component analysis is the suggestion that blood glucose levels may drop after irradiation. Some reports in the existing literature suggest a rise in glucose (24, 25) and some suggest no change in glucose (26) after irradiation. If a glucose drop postirradiation can be confirmed, it would be worthwhile to determine if a concomitant drop occurs in blood glucagon levels. A decrease in glucagon secretion from the pancreas could result in a decrease in glucose secretion from the liver, and this could explain decreases in blood glucose postirradiation.

The rationale of measuring the cyclooxygenase products 6-keto-$PGF_{1\alpha}$ and TXB_2 postirradiation stems from the knowledge that ionizing radiation can induce lipid peroxidation (27); this then can affect membrane phospholipase A_2 activity (28). Changes in phospholipase A_2 activity could result in changes in arachidonic acid production and the generation of lipoxygenase and cyclooxygenase products (29, 30). TXB_2 and 6-keto $PGF_{1\alpha}$ are cyclooxygenase products; and although the data are very preliminary, TXB_2 shows a tendency to rise at about 30 min postirradiation. If ionizing radiation does alter phospholipase A_2 activity, this would be interesting because the arachidonic acid cascade is a very important aspect of cellular activation (31).

Many of the systemic and central nervous system effects of neurotensin parallel the effects of radiation. Neurotensin can induce hypotension (32), suppress insulin secretion (33), and induce hypothermia (34). Likewise, radiation has been reported to cause hypotension (19, 21) and hypothermia (35) and, as shown in the data of this report, may suppress insulin secretion. Although the postirradiation plasma neurotensin levels in this report had not changed significantly, no measurements were made prior to 30 min postirradiation. Considering the parallels between the physiological responses to neurotensin and radiation, the levels of neurotensin at times earlier than 30 min postirradiation should be investigated.

Several protein blood components showed significant changes postirradiation. The drop in insulin at 30-60 min postirradiation appears promising: it may be related to the delay in gastric emptying in rats after irradiation (36). That insulin can abolish radiation-induced delay in gastric emptying is of particular interest (26). Although the relationship between gastric stasis and emesis is not clear, gastric stasis has been put forth as a condition that precedes vomiting. Since the postirradiation rise in glucose data does not corroborate the drop in insulin data, these data should be confirmed. The data

are not necessarily in conflict, particularly if the drop in insulin is paralleled by a drop in pancreatic secretion of glucagon. In any event the postirradiation levels of glucose, glucagon, and insulin should probably be carefully measured simultaneously.

Postirradiation increases in β-endorphin lipoproteins and ACTH may indicate that they can be derived from a common precursor (37). Two experiments with β-endorphin showed significant increases (Table 3): one at 10 and one at 30 min postirradiation. However, both of these components can vary greatly--depending on the emotional state of the animal, undetected injury or inflammation, or circadian rhythms--so the ACTH and β-endorphin assays would have to be repeated and confirmed with a much larger sample pool.

Two other protein blood components--gastrin and calcitonin--showed significant rises postirradiation. These rises may be related, in that the ability of calcitonin to regulate high gastrin through a feedback mechanism has been previously reported (38-40).

Vagal stimulation, an important aspect of emesis (2,9), can increase gastrin and HCl secretion (41). In addition, elevated gastrin can enhance gastric emptying, but this can be reversed by H_2-receptor blockade (42). This raises the possibility that elevated gastrin may be a response to radiation-induced gastric stasis. Calcitonin is an important regulator of plasma calcium (43), and the reduction of calcium by calcitonin can decrease calcium-dependent secretory mechanisms such as gastrin secretion.

Although the data of this report are preliminary, they do suggest directions of further investigation. Interrelationships of the various nonprotein, peptide, and protein blood components are too numerous to all be listed here. However, in addition to refinements and confirmation of the data presented here, further investigations should probably concentrate on the interrelationships of postirradiation changes in blood components. Demonstrated patterns of such interrelated changes may lead to positive insights into the biochemical basis of radiation-induced emesis and performance decrement.

CONCLUSION

We saw no evidence of increases in blood histamine postirradiation. Mast cells and basophils were refractory to direct irradiation in vitro; i.e., neither spontaneous nor induced release of histamine was affected by radiation. If mast cells and basophils are activated in vivo after irradiation, the direct cause is probably not radiation but some radiation-induced histamine-releasing factor. Also, if histamine is a component of radiation-induced emesis or performance decrement, it probably acts locally and is not endocrinelike in its effects.

Some evidence for postirradiation changes in arachidonic acid metabolism was present, but the evidence is not conclusive and requires further investigation.

Postirradiation changes were indicated in agents that affect gastric stasis. Insulin and glucose dropped and gastrin and calcitonin increased

postirradiation. Adrenocorticotropin and β-endorphin also showed some capacity to increase after irradiation.

The approach of this investigation was to determine if postirradiation changes in blood components could indicate the biochemical basis of radiation-induced emesis and performance decrement. Although preliminary, the data do indicate that the approach is valid. Conclusive progress in resolving this biochemical basis requires further investigation.

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